

REMARKS

1. Prior Art Issue (OA pp. 3-6)

The Examiner has made several obviousness rejections:

1. Claims 1, 14, 15, 22, 27, 28, 30 as obvious over Zittel (1995) or Saidi (1999) or Liedman (1998), in view of Wren (2001) or Asakawa (2001).
2. Claims 1-10 as obvious over the above references, further in view of Kojima (1999).
3. Claims 1-10 as obvious over the references of rejection #1, further in view of Hosoda (2003).

These rejections are respectfully traversed.

According to the Examiner, each of the primary references (Zittel, Saidi, Liedman) discloses that gastrectomy causes weight loss, and each of the secondary references (Wren, Asakawa) ghrelin stimulates appetite. The tertiary reference Kojima is cited for the sequence of Ghrelin, and the tertiary reference Hosoda for additional peptide sequences (ghrelin analogues).

All three rejections rely on the same secondary references. Wren investigated the effects of ghrelin on appetite and food intake in "nine healthy volunteers", not in gastrectomized individuals. Hence, the relevance of Wren to the instant claim 1, relating to treatment of a gastrectomized individual, is questionable.

While Wren teaches that ghrelin acts systemically and on the brain, it is clear from Asakawa (see below) that the person of ordinary skill in the art would have deemed such route of supposed action to be minor importance, and thought that it is the action of ghrelin in the stomach which is of principal concern.

As for Asakawa, as stated at page 4, lines 13-16 of the instant specification

Even though ghrelin has been found to be an appetite stimulatory signal, it has been noted that this stimulatory effect is lost after vagotomy (Asakawa, supra) giving rise to the notion that for a proper action of

ghrelin the presence of the stomach is required.

A vagotomy is the cutting of the vagus nerve; vagotomy "reduces the secretion of gastric juices and decreases physical activity of the stomach". A vagotomy is "often performed in combination with gastroenterostomy or partial gastrectomy", see Miller and Keane, *Encyclopedia and Dictionary of Medicine, Nursing, and Allied Heath* (3d. ed., 1983) at 1171 ("vagotomy").

See also page 1, lines 25-27 of the specification:

Gastrectomy, especially complete ventricle resection with roux-en-Y, results in section of extragastric vagal nerves, i.e., complete vagotomy. At present, more than three quarters of all patients who have undergone surgery for gastric cancer, have been subjected to total gastrectomy.

Additionally, the vagus nerve may be unintentionally damaged during the course of gastrectomy.

Because of the possibility of intentional or unintentional damage to the vagus nerve, consequent to gastrectomy, Asakawa would lead the person of ordinary skill to expect that ghrelin would not be as effective in stimulating appetite in gastrectomized individuals as in healthy subjects. And this was clearly recognized by applicant:

In contrast to the general belief, the present inventors have now found that ghrelin and its analogues are still effective in gastrectomized individuals, where potential local effects in the stomach do not operate. These findings are surprising as it has been reported that the stimulation of feeding and hypothalamic NPY expression by ghrelin analogues is dependent on intact vagal innervation (Asakawa, *supra*).

(page 4, lines 18-22).

New claims 39 and 40 further recite treatment (39) and inhibition (40), in a vagotomized individual, with basis at page 1, lines 25-27 and page 4, lines 18-22.

2. Unity (OA page 2)

In view of our showing above that the generic claims are patentable over the prior art, the species restrictions should be withdrawn.

3. Utility (OA pages 2-3)

The Examiner asserts that the claimed "prevention of loss of body weight and body fat and/or prophylaxis... of cachexia" are not well established utilities because:

- (1) it allegedly has not even been shown that ghrelin can mitigate loss of body weight or the state of cachexia, and
- (2) "it does not follow from mitigation that "outright prevention can be achieved".

3.1. As known from the prior art, gastrectomy causes weight loss and it is further clear from the application that loss of appetite and malabsorption may contribute to the observed weight loss (page 1-2). Cachexia is defined by the application (page 9) as a wasting disorder with symptoms such as weight loss and loss of appetite. It is further mentioned that cachexia is often associated with a chronic disease. The signs and symptoms observed in gastrectomized individuals include those seen in patients with cachexia. Although the disease leading to the gastrectomy may have been cured by the operation, the primary cause of the symptoms, i.e. the lack of certain parts (or all) of the stomach, must be considered a chronic condition which is mentioned above is a frequent feature of cachexia.

It is therefore possible to anticipate that a patient undergoing a gastrectomy will experience weight loss and/or cachexia in response to said surgery. Therefore alleviation of the symptoms e.g. treatment or prevention of weight loss and/or stimulation of appetite by administration of Ghrelin, must be considered a treatment or prevention of cachexia. It further follows that a skilled person based on the application will know how to use the invention, as Ghrelin can be administered to

gastrectomized individuals as described therein. It is further submitted that the application (example 1 and Figure 1-2) demonstrates an increase in body weight and fat pad weight in gastrectomized individuals.

3.2. The Examiner takes the position that the term "prevention", and perhaps also the term "prophylaxis", necessarily imply that the administration results in complete prevention of the condition in all individuals. However, that is not the general understanding of the term "prevention" in the medical art.

A search on the USPTO patents database revealed 21 patents containing the term "percent prevention" and 4 of "percentage prevention". (It unfortunately is not possible to search for "% prevention".)

On the NCBI Pubmed database, there are 820,112 hits for "% prevention", and 12,764 for "percent prevention". (We cannot readily search either database for phrases of the type "prevented in X% of cases".)

It is evident that if "prevention" necessarily meant absolute prevention, the phrase "% prevention" or "percent prevention" would be meaningless. We therefore believe that the Examiner is improperly limiting the meaning of "prevent". The aforementioned Encyclopedia, at page 94, defines "preventive" as "serving to avert the occurrence of; prophylactic", and page 920 defines "prophylactic" as tending to ward off disease".

Applicants teach that the typical loss of body weight in the first six months after gastrectomy is 10% (page 1, lines 31-35). It follows that if the ghrelin is administered prophylactically (i.e., prior to gastrectomy), that if the subsequent loss of body weight, if any, is less than 10%, that there has been a "prevention" of loss of body weight.

Claim 1 has been amended to limit it to treatment, thereby overcoming the rejection.

New claim 38 recites,

A method of inhibiting or treating the loss
of body weight or body fat, or the loss of

appetite, or the development of cachexia, attributable to gastrectomization, which comprises administering a prophylactically or the therapeutically effective amount of ghrelin or analogue thereof to an individual who has been gastrectomized, is being gastrectomized, or is scheduled to be gastrectomized.

The use of the term "inhibiting" rather than "preventing" makes it clear that absolute prevention is not required. It finds basis, although not in ipsissima verba, at, e.g., page 2, lines 18-19; page 1, lines 11-12; page 7, lines 6-7; page 5, lines 14-15; page 6, lines 1-6.

4. Indefiniteness Issues

Claims 15 and 22 have been amended.

Respectfully submitted,

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Enclosure

-Miller and Keane, Encyclopedia and Dictionary of Medicine, Nursing and Allied Health, title page and pp. 1171, 94.

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Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health

THIRD EDITION

*by the late Benjamin F. Miller, M.D., and
Claire Brackman Keane, R.N., B.S., M.Ed.*

*with 185 illustrations, including 16 color plates;
56 tables; 11 appendices*

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vaginopathy (vaj'i-nop'ah-the) any disease of the vagina.

vaginoperineal (vaj'i-no-per'i-ne'al) pertaining to the vagina and perineum.

vaginoperineorrhaphy (vaj'i-no-per'i-ne-or'ah-fe) suture of the vagina and perineum; colpoperineorrhaphy.

vaginoperineotomy (vaj'i-no-per'i-ne-ot'o-me) incision of the vagina and perineum.

vaginoperitoneal (vaj'i-no-per'i-to-ne'al) pertaining to the vagina and peritoneum.

vaginopexy (vah-ji'no-pek'se) colpopexy; vaginofixation; suturing of the vagina to the abdominal wall in cases of vaginal relaxation.

vaginoplasty (vah-ji'no-plas'te) colpoplasty; plastic repair of the vagina.

vaginotomy (vaj'i-not'o-me) colpotomy; incision of the vagina.

vaginovesical (vaj'i-no-ves'i-kal) pertaining to the vagina and bladder.

vagitus (vah-ji'tus) the cry of an infant.

v. uteri'nus, the cry of an infant in the uterus.

vagolysis (va-gol'i-sis) surgical lysis of the vagus nerve.

vagolytic (va'go-lit'ik) having an effect resembling that produced by interruption of impulses transmitted by the vagus nerve; parasympatholytic.

vagomimetic (va'go-mi-met'ik) having an effect resembling that produced by stimulation of the vagus nerve.

vagotomy (va-got'o-me) interruption of the impulses carried by the vagus nerve or nerves; so called because it was first performed by surgical methods. The surgical procedure is done as part of the treatment of gastric or duodenal ulcer and often is performed in combination with gastroenterostomy or partial gastrectomy. The vagus nerve stimulates gastric secretion and affects gastric motility. Vagotomy thus reduces the secretion of gastric juices and decreases physical activity of the stomach.

highly selective v., division of only those vagal fibers supplying the acid-secreting glands of the stomach, with preservation of those supplying the antrum as well as the hepatic and celiac branches.

medical v., interruption of impulses carried by the vagus nerve by administration of suitable drugs.

parietal cell v., selective severing of the vagus nerve fibers supplying the proximal two-thirds (parietal area) of the stomach; done for duodenal ulcer.

selective v., division of the vagal fibers to the stomach with preservation of the hepatic and celiac branches.

vagotonia (va'go-to'ne-ah) irritability of the vagus nerve, characterized by vasomotor instability, sweating, disordered peristalsis, and muscle spasms. adj., **vagoton'ic**.

vagotonin (va-got'o-nin) a preparation of hormone from the pancreas that increases vagal tone, slows the heart, and increases the store of glycogen in the liver.

vagotropic (va'go-trop'ik) having an effect on the vagus nerve.

vagovagal (va'go-va'gal) arising as a result of afferent and efferent impulses mediated through the vagus nerve.

vagus nerve (va'gus) the tenth cranial nerve; it has the most extensive distribution of the cranial

nerves, serving structures of the chest and abdomen as well as the head and neck.

Afferent fibers of the vagus nerve serve the mucous membrane of the larynx, trachea, and bronchi, lungs, arch of the aorta, esophagus, and stomach. Some of the functions affected by this nerve are coughing, sneezing, reflex inhibitions of the heart rate, and the sensation of hunger.

Motor fibers of the vagus nerve are concerned with swallowing, speech, peristalsis, and secretions from the glands of the stomach and the pancreas and contractions of the trachea, bronchi, and bronchioles.

valence (va'lens) the numerical measure of the capacity to combine; in chemistry, an expression of the number of atoms of hydrogen (or its equivalent) that one atom of a chemical element can hold in combination, if negative, or displace in a reaction, if positive; in immunology, an expression of the number of antigenic determinants with which one molecule of a given antibody can combine or of the number of different organisms or antigens attacked by a vaccine or antiserum.

valgus (val'gus) [L.] bent outward; twisted; denoting a deformity in which the angulation is away from the midline of the body, as in talipes valgus.

valine (va'lēn) a naturally occurring amino acid, one of those essential for human metabolism.

valinemia (val'i-ne'me-ah) hypervalinemia; elevated levels of valine in the blood and urine.

Valisone (val'i-sōn) trademark for preparations of betamethasone valerate; an anti-inflammatory.

Valium (val'e-um) trademark for a preparation of diazepam, an anxiolytic and skeletal muscle relaxant.

vallate (val'at) having a wall or rim; rim-shaped.

vallecula (vah-lek'u-lah), pl. *valleculae* [L.] a depression or furrow.

v. cerebel'li, a longitudinal fissure on the inferior cerebellum, in which the medulla oblongata rests.

v. syl'vii, a depression made by the fissure of Sylvius at the base of the brain.

v. un'guis, the sulcus of the matrix of the nail.

vallestril (val-les'tril) trademark for a preparation of methallenestril, an estrogenic compound.

Valleir's points (vahl-lāz') tender points along the course of certain nerves in neuralgia; called also *puncta dolorosa*.

Valley fever coccidioidomycosis.

valproic acid (val-pro'ik) an anticonvulsant used for the control of absence seizures.

Valsalva's maneuver (val-sal'vahz) 1. increase of intrathoracic pressure by forcible exhalation against the closed glottis. The maneuver causes a trapping of blood in the great veins, preventing it from entering the chest and right atrium. When the breath is released, the intrathoracic pressure drops and the trapped blood is quickly propelled through the heart, producing an increase in the heart rate (tachycardia) and the blood pressure. Immediately after this event a reflex bradycardia ensues. Valsalva's maneuver occurs when one strains to defecate and urinate, uses his arm and upper trunk muscles to move up in bed, or strains during coughing, gagging, or vomiting. The increased pressure, immediate tachycardia, and reflex bradycardia can

require assisted ventilation. When it is delivered at this phase of the respiratory cycle it is called positive-end-expiratory pressure (PEEP). Or, it can be delivered continuously to patients who are breathing spontaneously, in which case it is called continuous positive airway pressure (CPAP). PEEP is believed to increase the level of oxygen in the arterial blood and thereby reduce the amount of oxygen that must be given supplementally. However, it also enhances problems resulting from increased pressure within the thorax. CPAP also holds the smaller airways and alveoli open and limits atelectasis, and has the advantage of presenting fewer problems related to increased airway pressures.

Regardless of the mode of cycling and whether the machine provides assisted or controlled ventilation or both, all ventilators provide for the humidification of inspired air and the measurement of expired volumes. (See also INTERMITTENT POSITIVE-PRESSURE BREATHING.)

PATIENT CARE. Regardless of the model and capabilities of the mechanical ventilator being used in the treatment of a patient with inadequate ventilation, there are certain general principles that are basic to the competent care of that patient. It is essential that all those who accept responsibility for the care of the patient be fully aware of the physiologic effects of mechanical ventilation, particularly in regard to the relationship between the distribution of inspired air in the lung and the status of the BLOOD GASES and pH. A major contribution of mechanical ventilation should be the normalization of blood gases and avoidance of the extremes of ACIDOSIS and ALKALOSIS. Thus careful monitoring of the blood gases and the pH is an essential part of patient care during mechanical ventilation.

A second consideration in patient care and assessment of the effects of mechanical ventilation is that of its influence on circulation. It is apparent that increased intrathoracic pressure can interfere with the flow of blood through the great vessels and the chambers of the heart. The ultimate effect can be a pooling of blood in the veins and capillaries of the abdominal organs and a resultant vascular collapse that is sometimes called respirator shock. Frequent determinations of pulse rate and blood pressure are necessary to detect early development of this condition and correction of pressure levels to forestall shock. It should be noted that interference with the venous return to the right side of the heart can bring about a therapeutic effect in patients with pulmonary EDEMA. Thus a potentially hazardous side effect of an increase in intrathoracic pressure can be of benefit to the patient when used judiciously by a physician who is knowledgeable about all aspects of ventilatory therapy.

A third consideration is that of the effects of mechanical ventilation on the body fluid-antidiuretic hormone balance. It has long been recognized that pressure breathing, both positive and negative, influences the production of the antidiuretic hormone, causing an excess of this hormone and a resultant retention of water. If not corrected, the situation can lead to pulmonary edema and further interference with the patient's ventilation. The possibility of such an eventuality demands that accurate records be kept of the patient's intake and output and that a safe balance be maintained.

A thorough knowledge of the apparatus being

used for mechanical ventilation is vital to competent care of the patient. No one should attempt to give patient care without prior instruction in the purpose of the machine and the physiologic and physical principles upon which it operates.

TRACHEOSTOMY care is of vital importance when the patient is being maintained on a respirator with controlled ventilation and positive pressure is being delivered via a tracheostomy tube. Suction is applied as necessary and some method for moisturizing the air is provided. In fact, whether the patient has a tracheostomy or not, the air passages must be kept moist whenever a respirator is used for a prolonged period.

If AEROSOL medications are administered by use of a respirator, it is important to know the type of medication being used, its desired effects and the signs and symptoms of overdosage or toxic side effects. When such symptoms appear the rate of nebulization requires adjustment.

The psychologic implications of the use of a respirator are manifold. If he is conscious or semiconscious, the patient is aware that the machine is concerned with maintaining his very "breath of life" and he is understandably apprehensive about its use and effects on his breathing. When a respirator is used for a brief period as a means of therapy, the patient can be told that he can control the cycle by the slightest effort on his part. Once he understands the way the machine works and his questions are answered to his satisfaction his fears can be allayed. The patient who is partially or totally dependent on a respirator will need more reassurance. He should be assured that someone will be near at all times in case the apparatus needs adjusting. Much of his panic and fear can be relieved if the nursing staff exercises patience and maintains a calm attitude when helping him adjust to the respirator.

Weaning from the Ventilator. Gradual withdrawal of the support of the ventilator ("weaning") begins as soon as the patient's blood gases, spontaneous breathing capabilities, and clinical status indicate that he may be able to start breathing on his own. Some patients view with alarm the prospect of trying to breathe without the aid of the ventilator while others may be overenthusiastic and wish to end their dependence on the machine before they are ready to do so. Difficulties are more likely to develop in those who have had prolonged controlled ventilation than in those who have had assisted ventilation for a short period of time.

Prior to the actual removal of ventilatory assistance the patient should be taught abdominal breathing and informed that a deep controlled breathing pattern will be more advantageous than rapid shallow breaths. He will need calm assurance that he will not be expected to endure any distress beyond his capability to cope with it, and that a person in whom he has confidence will remain with him while he is off the respirator.

It is recommended that weaning be initiated during the morning hours when the patient is most rested and relaxed. During the time the ventilator is first removed, the patient may be given humidified oxygen, or as in the case of the tracheotomized patient, warmed and humidified oxygenated air. Such measures will enhance the patient's tolerance to the weaning process. As his tolerance increases, the period of time he is off the ventilator is lengthened. Once he is able to breathe adequately independently of the ventilating machine, a simple ventilator may be kept close at hand in the event the patient should